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Risk factors for cardiovascular events in hospitalized patients with community-acquired pneumonia

Allen T. Griffin *, Timothy L. Wiemken, Forest W. Arnold

School of Medicine, Department of Medicine, Division of Infectious Diseases, University of Louisville, 501 East Broadway, Suite 380, Louisville, KY 40292, USA

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SUMMARY

Background: An increased risk of cardiovascular complications has been found in those with community-acquired pneumonia (CAP). Preliminary data suggest that pneumococcal pneumonia, more severe pneumonia, older age, renal disease, hypoalbuminemia, and inpatient sliding scale insulin administration contribute to risk. The objective of this study was to ascertain additional factors influencing cardiovascular events in CAP.

Methods: This investigation was a retrospective cohort study of inpatients with CAP. Outcomes evaluated were development of a cardiovascular event during hospitalization, defined as acute pulmonary edema, cardiac arrhythmia, or myocardial infarction. Those with and without events were compared across cardiovascular- and pneumonia-specific variables by logistic regression to ascertain factors that independently increase risk or reduce risk.

Results: Of 3068 inpatients with pneumonia, 376 (12%) developed a cardiovascular event. Hyperlipidemia, more severe pneumonia, and *Staphylococcus aureus* or *Klebsiella pneumoniae* as etiologies were associated with increased risk, while statin use was associated with decreased risk.

Conclusions: This study highlights variables in CAP patients that should make clinicians vigilant for the development of cardiac complications. Additional research is needed to determine if statins attenuate cardiac risk in CAP.

1. Introduction

While community-acquired pneumonia (CAP) may result in morbidity and mortality as a direct function of an infectious agent's deleterious effects on the respiratory system, those with CAP are known to develop additional complications extraneous to the lungs.[1] These complications may not be directly related to the pathogen itself, but are postulated to be due in part to the inflammatory response that ensues.[2] Among other sequelae, evidence has suggested an increased risk of cardiovascular events, such as myocardial infarction, in those with CAP.[3,4] Preliminary data have demonstrated that infection with the pneumococcus,[5,6] older age, a previous cardiac history, severe pneumonia,[2,6] chronic kidney disease, hypoalbuminemia,[6] and sliding scale insulin administration during a CAP episode[7] may contribute to developing cardiac incidents in CAP. In contrast, other reports have suggested improved outcomes in general in the setting of CAP with medications mitigating cardiovascular disease, such as statins and angiotensin converting enzyme (ACE) inhibitors,[8] but no study has evaluated cardiovascular events in the setting of CAP with reference to such medications. As a result, the objective of this study was to ascertain additional risk factors or protective factors influencing cardiovascular events in CAP, including medications prescribed specifically for cardiovascular diseases, and to clarify previously defined risk factors for such events.

2. Methods

2.1. Study design and population

This study was a secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) database on CAP, a multicenter, retrospective, international cohort study of inpatients from 80 centers in 13 countries. Patients with a confirmed diagnosis of CAP were entered into the database from June 1, 2011 to November 12, 2012. Data procured for CAPO were collected on a case report form, entered into a computer database, and then reviewed for quality assurance before final acceptance into the database. Institutional review board evaluation was performed at each of the sites from which patients were sampled. Informed consent was waived due to the retrospective nature of this investigation.

Inclusion criteria were age ≥16 years and confirmed CAP. CAP was verified if a new infiltrate on chest X-ray was present with any

* Corresponding author. Tel.: +1 502 852 1148; fax: +1 502 852 1147.
E-mail addresses: atgrif01@louisville.edu, allen.griffinmd@gmail.com (A.T. Griffin).

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of the following: leukocyte count $>10 \times 10^9$ cells/l, $<4 \times 10^9$ cells/ml, or >5% bands; new onset or increased cough; or temperature $\geq$37.8 °C or $\leq$35.6 °C. Patients were excluded if pneumonia developed 48 h or more after admission. CAP severity was ascertained by the Pneumonia Severity Index (PSI).[9] Etiologic organisms of pneumonia were discerned primarily by blood or sputum culture. Some institutions performed urinary antigen testing (*Legionella pneumophila* and *Streptococcus pneumoniae*), PCR testing (*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, and respiratory viruses), and sputum culture on buffered charcoal yeast extract agar (BCYE) or direct fluorescent antibody staining of sputum for *Legionella* species.

2.2. Study definitions

A cardiovascular event was defined as acute pulmonary edema, new onset cardiac arrhythmia, exacerbation of a preexisting arrhythmia, or myocardial infarction. All events were confirmed by an attending physician at the time they transpired and were required to be documented in the medical records to be considered present for this analysis. Pulmonary edema was diagnosed by a combination of clinical exam findings (such as jugular venous distension), radiologic evidence, and/or elevated brain natriuretic peptide levels. For an arrhythmia to be considered exacerbated, new clinical signs or symptoms, such as chest pain, dyspnea, or cardiac arrest, had to accompany the arrhythmia and be deemed by the treating physician to be due to the arrhythmia. Myocardial infarction was verified by electrocardiogram aberrations and elevated cardiac biomarkers including myocardial specific creatine kinase and/or cardiac troponins. To be considered relevant to the current episode of pneumonia, all cardiovascular events had to transpire upon admission for CAP or at some time during the concurrent hospitalization for CAP. If a patient developed more than one cardiac incident during hospitalization, the case in question was counted as a single cardiac event in analyzing the primary outcome. Comorbidities, such as hyperlipidemia or previous cardiac disease, were defined as present if documented in the medical records by a medical provider.

2.3. Study outcomes

The primary outcome assessed in this study was development of a cardiovascular event during admission for CAP. Secondary outcomes included in-hospital mortality and 28-day mortality, the cumulative number of deaths from admission until 28 days after admission, regardless if the patient was discharged from the hospital. Categories of variables collected as potential confounders of cardiovascular events and used in multivariate analyses were: age, sex, history of cardiovascular disease prior to pneumonia admission, history of atrial fibrillation prior to admission, current smoking status, family history of cardiac disease, use of cardiovascular medicines (anticoagulants (heparin or warfarin), aspirin, alternative antiplatelet agents (clopidogrel, ticlopidine), beta-blockers, ACE inhibitors, or statins), genus and species of infecting bacteria, initiation of empiric therapy within 8 h of pneumonia diagnosis, empiric macrolide therapy during pneumonia admission (erythromycin, clarithromycin, or azithromycin), empiric quinolone therapy during pneumonia admission (moxifloxacin, levofloxacin, ciprofloxacin, ofloxacin, gemifloxacin, or lomefloxacin), albumin level on admission, pneumonia severity by PSI, and presence of bacteremia related to pneumonia. For this analysis, use of a medication was defined as use during the current hospitalization for pneumonia or use as an outpatient prior to admission. Empiric antibiotic therapy was denoted as the antibiotic regimen begun within the first 48 h of admission before an etiologic agent was identified.

2.4. Statistical analyses

Chi-square or Fisher's exact tests were used to compare baseline categorical characteristics of those with and without cardiovascular events, while the Mann–Whitney *U*-test was used to compare continuous characteristics between the two groups.

To create a predictive model to evaluate variables significantly associated with cardiovascular events in hospitalized patients with CAP, multivariable logistic regression models were employed. Rather than eliminating patients with missing values for any particular variable, we used bootstrapped additive imputation models to create datasets with complete data for every patient. A total of 20 imputed datasets were created to obtain the most valid variance estimates. In each dataset, all variables were analyzed for collinearity using variance inflation factor and tolerance statistics.

Next, these 20 datasets were each subjected to a purposeful selection algorithm to create a final best-fit predictive logistic regression model.[10] The variables collected as potential confounders of cardiovascular events, as previously elucidated, were the ones included in the purposeful selection algorithm. Briefly, the purposeful selection algorithm initially selects variables with bivariate *p*-values of $\leq$0.25, and fits a model based on backwards elimination. Next, variables eliminated by backwards elimination are further assessed for potential confounding along with the remaining variables, and any included variable with a $\geq$15% change in the regression coefficient is replaced in the model. Finally, variables initially excluded based on the bivariate analysis are further assessed for confounding with the included variables and are similarly added back to the model if the regression coefficients change by $\geq$15%. In this analysis, variables remaining in the purposeful selection of each of the 20 datasets were noted, and any variables remaining in more than 50% of the purposefully selected models were included in a final logistic regression model.

R version 2.15.1[11] and SAS version 9.3 (SAS Inc, Cary, NC) were used for all analyses. The Hmisc package was used for multiple imputation following accepted procedures.[12] Except as specified previously in the initial selection of variables in the purposeful selection algorithm, *p*-values $\leq$0.05 were considered significant.

3. Results

Of 3068 patients with CAP, 376 (12%) presented with at least one cardiovascular event upon admission or subsequently developed an event during hospitalization. However, in total, 435 events occurred, as some patients had more than one cardiovascular incident during hospitalization. The most common event to transpire was exacerbation of a previously diagnosed arrhythmia (Table 1). Those with a cardiac complication were more likely to be older and to have had a preexisting cardiac history, atrial fibrillation, hypertension, or hyperlipidemia. Furthermore, they were more likely to have been administered empiric macrolide therapy or to have been prescribed aspirin or another antiplatelet, beta-blockers, or ACE inhibitors as a

Table 1
Distribution of cardiovascular events by category of event[a]

Event	*n* (%)	Present on admission	Developed during hospitalization
	(*n* = 435)	(*n* = 188)	(*n* = 247)
New onset arrhythmia	179 (41)	70 (37)	109 (44)
New onset pulmonary edema	127 (29)	64 (34)	63 (26)
Worsening of preexisting arrhythmia	73 (17)	28 (15)	45 (18)
Myocardial infarction	56 (13)	26 (14)	30 (12)

[a] All values are given as number (*n*) of events by category (% of total events).

Table 2
Baseline patient characteristics in those with and without a cardiovascular event during admission[a]

Variable	Cardiovascular event *n* (%) (*n* = 376)	No cardiovascular event *n* (%) (*n* = 2692)	*p*-Value
Demographics			
Age, years, median (IQR)	78 (21)	64 (33)	<0.001
Male sex	217 (58)	1572 (58)	0.823
Comorbidities			
Cardiovascular disease	49 (13)	180 (7)	<0.001
Atrial fibrillation	66 (18)	176 (7)	<0.001
Arterial hypertension	139 (37)	706 (26)	<0.001
Hyperlipidemia	61 (16)	283 (11)	0.002
Current smoking	55 (15)	520 (21)	0.006
Family history of CAD	28 (7)	167 (6)	0.366
Albumin, mg/dl, median (IQR)	3.2 (0.7)	3.2 (0.9)	0.390
Cardiovascular medicine use			
Warfarin	20 (5)	108 (4)	0.269
Heparin	7 (2)	28 (1)	0.180
Aspirin	77 (20)	345 (13)	<0.001
Antiplatelet therapy	22 (6)	80 (3)	0.008
Beta-blocker therapy	70 (19)	325 (12)	0.001
ACE inhibitor therapy	66 (18)	370 (14)	0.058
Statin therapy	43 (11)	294 (11)	0.792
Pneumonia etiology and bacteremia			
Streptococcus pneumoniae	48 (13)	427 (16)	0.128
Moraxella catarrhalis	0 (0)	7 (0)	1.000
Haemophilus influenzae	6 (2)	28 (1)	0.298
Staphylococcus aureus	20 (5)	74 (3)	0.010
Escherichia coli	6 (2)	19 (1)	0.114
Klebsiella pneumoniae	7 (2)	12 (0)	0.005
Legionella pneumophila	3 (1)	39 (1)	0.470
Pseudomonas aeruginosa	5 (1)	32 (1)	0.800
Bacteremia	46 (12)	315 (12)	0.733
Antibiotic therapy and severity of disease			
Therapy within 8 h	257 (81)	827 (82)	0.828
Empiric macrolide therapy	302 (80)	2027 (75)	0.034
Empiric quinolone therapy	140 (41)	827 (36)	0.102
PSI, median (IQR)	124 (51)	93 (60)	<0.001

CAD, coronary artery disease; ACE, angiotensin converting enzyme; IQR, interquartile range; PSI, Pneumonia Severity Index.
[a] All values are given as number (%) unless otherwise specified.

result of medical comorbidities. *Staphylococcus aureus* and *Klebsiella pneumoniae* were more likely pathogens in this group, and pneumonia severity was greater at baseline in those with an event (Table 2).

After the purposeful selection algorithm was executed on all of the variables from Table 2, those remaining in the final best-fit logistic regression model included age, male gender, hyperlipidemia, statin therapy, *S. aureus* or *K. pneumoniae* as etiologies of CAP, empiric macrolide therapy, and pneumonia severity. However, only hyperlipidemia, greater pneumonia severity, and *S. aureus* or *K. pneumoniae* as etiologies of CAP remained as significant predictors of a cardiovascular event, while statin therapy was associated with a lower risk of an event (Table 3). For the risk factors found to be statistically significant in the final regression model, the distribution by type of cardiovascular incident for each factor is shown in Table 4.

Table 3
Results of the multivariate logistic regression analysis[a]

Variable	Odds ratio (95% CI)	*p*-Value
Age	1.01 (1.00–1.02)	0.137
Male gender	0.84 (0.66–1.08)	0.177
Hyperlipidemia	2.01 (1.33–3.05)	0.001
Statin therapy	0.52 (0.33–0.84)	0.007
Staphylococcus aureus	1.61 (1.02–2.86)	0.050
Klebsiella pneumoniae	2.95 (1.05–8.68)	0.050
Empiric macrolide therapy	0.81 (0.64–1.03)	0.089
PSI	1.02 (1.01–1.02)	<0.001

95% CI, 95% confidence interval; PSI, Pneumonia Severity Index.
[a] These variables represent the ones retained in the final logistic regression model after the purposeful selection algorithm was executed.

Finally, those patients developing cardiovascular incidents during admission were significantly more likely to die during hospitalization or at 28 days after admission. During admission, 28% of the event group died compared to 8% of the non-cardiovascular event group ($p < 0.001$). Cumulatively at 28 days from admission, 36% of the total cardiovascular event group died compared to 10% in the comparison group ($p < 0.001$).

4. Discussion

The present study demonstrated an increased risk of cardiovascular sequelae in the context of CAP in those patients who had a history of hyperlipidemia, had a greater pneumonia severity, or had *S. aureus* or *K. pneumoniae* as etiologies of pneumonia. In addition, this study illustrated a trend for a greater risk in those who were older. Those patients having cardiac complications were more likely to die during hospitalization or at 28 days. In contrast, this analysis found statins to be protective with regards to developing cardiac events, while suggesting a trend for less risk with empiric macrolides. However, additional medications, including those that have effects on the cardiovascular system such as beta-blockers and ACE inhibitors, were not demonstrated to influence cardiac sequelae. These results are important because they suggest that certain at-risk patients (those with hyperlipidemia, higher pneumonia severity, *S. aureus* or *K. pneumoniae*, and older age) deserve vigilance on the part of clinicians for developing cardiac complications in the setting of CAP and likely require additional cardiac monitoring to recognize these events early and intervene appropriately. These findings also suggest medications (statins) that should be further investigated as agents to attenuate events. To our knowledge, this is the first study to delineate hyperlipidemia, *S. aureus* or *K. pneumoniae* as etiologies, or statin use as potential mediators of cardiovascular events in CAP.

The elevated cardiovascular risk with hyperlipidemia elaborated in the current study is thought to be due to the association of hyperlipidemia with atherosclerotic plaque that may become

Table 4
The most common cardiovascular events by risk factor found to be statistically significant in the final regression model[a]

Risk factor	Cardiovascular event			
	New onset arrhythmia, *n* (%)	Pulmonary edema, *n* (%)	Worsening arrhythmia, *n* (%)	Myocardial infarction, *n* (%)
Hyperlipidemia (*n* = 72)	29 (40)	19 (26)	6 (8)	18 (25)
Staphylococcus aureus (*n* = 24)	11 (46)	5 (21)	4 (17)	4 (17)
Klebsiella pneumoniae (*n* = 11)	4 (36)	1 (9)	2 (18)	4 (36)
PSI class IV or V (*n* = 364)	146 (40)	113 (31)	53 (15)	52 (14)

PSI, Pneumonia Severity Index.
[a] All values are number of a given cardiovascular event per risk factor (% of total events for that risk factor).

unstable during infection.[13] Furthermore, stabilization of this plaque by statin therapy,[14] or reduction of the subsequent cytokine storm by these medicines,[15] may have contributed to the attenuated risk in those administered statins.

The increased event rate seen with more severe pneumonia in this study, though not robust, and the increased event rate illustrated with *S. aureus* and *K. pneumoniae*, are likely explained by the extreme cytokine cascade that ensues in these settings. This inflammation may contribute directly to plaque destabilization,[13] progression of atherosclerosis as a result of prolonged aberrations in lipoprotein profiles,[16] and predisposition to arrhythmias.[17]

Despite the association of macrolide antibiotics with QTc prolongation,[18] they were not linked to cardiac events in this study, and in fact, appeared to be associated with a decreased risk. It is postulated that the potential anti-inflammatory properties of macrolides in respiratory infection[19] and their activity against atypical bacteria that may comprise coronary plaques,[20] may explain the trend for lower cardiac incidents seen with such therapy.

The results of the current study are concordant with past evidence that has found elevated cardiac risk in the setting of CAP related to increased age and greater pneumonia severity.[2,6] However, in contrast to previous literature that has found an overt cardiac history to be a risk for events,[2,6] the current study only found a common accompaniment of prior cardiovascular disease, hyperlipidemia, to be a risk, and as a result, indirectly replicates the findings of increased cardiovascular occurrences and a prior cardiac history. It is plausible that hyperlipidemia and atherosclerotic plaque are the principle determinants of cardiac events in the context of CAP in those with prior cardiac histories. While the current analysis did not find the pneumococcus to be a risk for cardiac sequelae like previous reports,[5,6] related virulent pathogens, including *K. pneumoniae* and *S. aureus*, were found to be risks. It may be that if the extensive list of pathogens included in the current investigation had been included in other analyses, the association in these past studies with the pneumococcus and cardiac complications may have become attenuated.

The current study is the first to our knowledge to illustrate the protective effects of statins in relation to cardiac events and CAP. Given that the level of evidence we present is observational, we could not eliminate the contribution of confounders such as the healthy user effect that may explain these results with statins. However, statins have also been shown to reduce morbidity and mortality in general in the setting of CAP.[8] The potential reduction of cardiac events seen in the current analysis associated with statins could be one of the mechanisms for the reduced morbidity and mortality in pneumonia elucidated in other studies addressing CAP and statins.[8] Further supporting the results of the current study related to statins is basic science data illustrating attenuation of cardiovascular system dysfunction with statin administration in acute lung injury created by endotoxin.[21] The suggestion of beneficial cardiac effects with macrolides is also novel, but is preliminary and difficult to interpret. Recent studies with macrolides illustrating both increased cardiac sequelae, particularly arrythmias,[22,23] and lack of increased sequelae exist.[24] One putative explanation for these disparate results in the literature and the findings in the present study that differ from the former two studies, is that macrolides may have differential effects depending on the type of cardiac event. Events with a prominent inflammatory component like myocardial infarction[13] may be reduced, while events linked to aberrations in the cardiac conduction system may be increased. With the current analysis, we were not able to unravel this postulated bidirectional cardiac effect of macrolides.

The results of the current analysis are generalizable to the general adult CAP population given the multiple centers included and few exclusion criteria employed. The diverse population under study in CAPO, as well as the rigorous data collection process and statistical analysis in this study, are also clear strengths. Furthermore, the inclusion of multiple potential variables affecting cardiac events, such as cardiovascular medications, macrolide use, and additional pathogens that have not been included in other studies, is a strength.

A limitation, however, is the retrospective design; thus, given the lack of randomization to medications like statins, causation cannot be inferred, leaving explanations such as the healthy user bias to be considered. In addition, recently approved cardiovascular medications, such as dabigatran and rivaroxaban, angiotensin receptor blockers, anticoagulants other than warfarin and heparin, and potential modulators of events like sliding scale insulin,[7] were not evaluated, as these variables were not previously procured in the CAPO database. Furthermore, factors affecting volume status and resultant pulmonary edema in particular, such as acute kidney injury and degree of volume resuscitation required for those in severe sepsis, were also not evaluated for similar reasons. Finally, while specific criteria for the diagnosis of cardiac events were utilized in most instances, the diagnosis of a cardiac event was ultimately left to the treating physician and confirmed retrospectively.

Further investigation is needed to replicate and extend these results. In particular, prospective, observational studies concerning the relationship of macrolides to cardiac disease are required given the present findings and the controversy that exists in the literature related to these antibiotics. Future study should endeavor to discriminate risks and benefits of macrolides in relation to the category of cardiac event. Given that ample observational evidence has illustrated the benefit of statins in the context of pneumonia in general and that the current study showed a reduced risk of cardiac events in those patients on statins, a randomized controlled trial investigating statin therapy prescription at the time of pneumonia diagnosis is warranted.

In summary, we found a previous diagnosis of hyperlipidemia, greater pneumonia severity, and *S. aureus* or *K. pneumoniae* as causes of pneumonia to be risks for cardiac events in CAP. Patients with these complications were more likely to die during hospitalization or at 28 days. In contrast, previous or current use of statins was protective, while there was a trend for less risk with macrolides. These results are important because they suggest patient factors of which clinicians should be cognizant in order to identify cardiac events early in at-risk patients and intervene in a timely fashion. Telemetry or frequent ECG monitoring seems particularly prudent in those harboring multiple risk factors. Finally, these findings argue for further study on statins and macrolides concerning cardiac events in the setting of pneumonia.

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